Combination treatment with trimetazidine and diltiazem in stable angina pectoris

S C Manchanda, S Krishnaswami

Abstract

Objective—To assess antianginal efficacy and possible adverse haemodynamic effects of combination treatment with trimetazidine and diltiazem in patients with stable angina.

Design—Double blind, randomised, placebo controlled trial of four weeks duration.

Setting—Outpatient department of two Indian hospitals.

Subjects—64 male patients with stable angina, uncontrolled on diltiazem alone.

Interventions—Diltiazem 180 mg and trimetazidine 60 mg, or diltiazem 180 mg and placebo daily.

Main outcome measure—Change in exercise time to 1 mm ST segment depression.

Results—33 patients (55%) had no exercise induced angina at 3 mm ST segment depression at inclusion in the study (silent ischaemia). Intention to treat analysis showed that of 32 patients in each treatment group, the number (%) of patients responding to trimetazidine compared to placebo was: for anginal attacks, 28 (87.5) v 15 (46.9), $p < 0.001$; for exercise time to 1 mm ST segment depression, 21 (65.6) v 9 (28.1), $p < 0.003$; for exercise time to angina, 12 (37.5) v 5 (15.6), $p < 0.05$; and for maximum work at peak exercise, 17 (53.1) v 8 (25), $p < 0.02$. Compared to placebo, there was net improvement with trimetazidine in mean anginal attacks of 4.8/week (95% confidence interval (CI) 7.5 to 2.1; $p < 0.002$); in mean exercise times at 1 mm ST segment depression of 94.2 seconds (95% CI 182.8 to 5.6; $p < 0.05$), and at onset of angina of 113.1 seconds (95% CI 181.6 to 44.6; $p < 0.02$); and in mean maximum work at peak exercise of 1.4 metabolic equivalents (95% CI 2.4 to 0.3; $p < 0.05$).

Conclusions—Patients with stable angina uncontrolled with diltiazem had a clinically important improvement after combination treatment with trimetazidine, without adverse haemodynamic events or increased side effects.

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Keywords: trimetazidine; diltiazem; blood pressure; stable angina; treatment

Department of Cardiology, All India Institute of Medical Sciences, New Delhi, India
S C Manchanda

Department of Cardiology, Christian Medical College Hospital, Vellore, India
S Krishnaswami

Correspondence to:
Dr Manchanda, Department of Cardiology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110 029, India.

Patients with stable angina pectoris are often effectively controlled by monotherapy with nitrates, β blockers, or calcium entry blockers. When symptoms intensify, these drugs are used in combination. However, there are problems with their use because of adverse effects, contraindications, and the fact that they are not always effective,[1] and even triple drug therapy may not confer a clear clinical advantage.[2] Alternative treatment with coronary artery bypass grafting (CABG) and percutaneous transluminal coronary angioplasty (PTCA) is effective, but up to 28% of patients undergoing CABG, and 75% undergoing PTCA, require at least one antianginal drug after six months.[3] Further, these procedures are unaffordable or inaccessible for most patients in developing countries like India, where an estimated 40 million people suffer from coronary artery disease.[4] There is therefore a continuing need for effective, safe, and acceptable antianginal drug treatment.

Trimetazidine—1-(2,3,4 trimethoxybenzyl)-piperazine dihydrochloride (Flavedon 20)—is a lesser known member of a new class of antianginal drugs,[5] although it has been used in many Asian and European countries for several years. Its mode of action is different from β blockers, calcium entry blockers, and nitrates. Unlike these antianginal agents, which affect haemodynamic determinants of the myocardial oxygen supply–demand balance,[1] trimetazidine partly prevents intracellular metabolic changes such as depletion of adenosine triphosphate (ATP) and phosphocreatine, accumulation of protons, and toxic free radical generation which result from ischaemia and reperfusion in the myocardium.[6]

In controlled studies, the antianginal efficacy of trimetazidine in monotherapy was greater than placebo,[7] and equal to nifedipine,[8] or propranolol,[9] with no effect on heart rate and blood pressure and no major adverse effects.[7] Diltiazem, a calcium entry blocker with confirmed efficacy in the treatment of stable angina, increases coronary blood flow and reduces myocardial oxygen demand by peripheral arterial vasodilatation and a negative inotropic effect.[1] The action of trimetazidine could enhance the antianginal efficacy of diltiazem when the two are used in combination, without increasing adverse haemodynamic effects such as reflex tachycardia, bradycardia, hypotension, or fatigue that occur with other drug combinations (such as β blockers with calcium entry blockers or nitrates).[1]

In this two centre, double blind, randomised, placebo controlled trial, we assessed combination treatment with trimetazidine and diltiazem for patients with stable angina.

Table 1 Baseline characteristics of patients according to study group

Characteristic	Trimetazidine and diltiazem (n=32)	Placebo and diltiazem (n=32)
Age (years (SD))	56.6 (7.5)	55.0 (5.0)
Male sex (%)	32 (100)	32 (100)
Indian race (%)	32 (100)	32 (100)
NYHA functional class*		
2 (%)	21 (65.6)	23 (71.9)
3 (%)	11 (34.4)	9 (28.1)
Duration of stable angina (months (SD))	39.0 (37.1)	27.1 (24.0)
Patients with silent ischaemia† (%)	16 (50)	8 (25)
History of myocardial infarction‡ (%)	8 (25)	8 (25)
Previous treatment for angina		
Percutaneous transluminal coronary angioplasty (%)	2 (6.3)	0 (0)
Long acting nitrates (%)	14 (43.7)	15 (46.9)
β Blockers (%)	26 (81.3)	25 (78.1)
Calcium channel antagonists (%)	19 (59.4)	15 (46.9)
Two drug combination (%)	16 (50)	19 (59.4)
Three drug combination (%)	5 (15.6)	5 (15.6)
Resting heart rate (per min (SD))	84.0 (13.8)	80.2 (12.5)
Systolic blood pressure (mm Hg (SD))	139.4 (18.1)	136.8 (17.2)
Diastolic blood pressure (mm Hg (SD))	85.5 (10.9)	85.3 (8.8)
Total cholesterol (mmol/l (SD))	5.47 (0.81)	5.83 (1.28)
HDL cholesterol (mmol/l (SD))	1.00 (0.13)	1.01 (0.15)
Total triglyceride (mmol/l (SD))	1.97 (0.92)	1.98 (0.75)
Fasting blood glucose (mmol/l (SD))	5.52 (1.27)	5.78 (1.49)
Serum creatinine (μmol/l (SD))	88.4 (8.8)	79.6 (8.8)

HDL, high density lipoprotein.
*New York Heart Association classification.[10]
†No treadmill exercise induced angina at 3 mm ST segment depression.
‡Earlier than three months before starting study treatment.

Methods

PATIENT SELECTION

The study protocol was approved by the hospital ethics committee of both centres. Ambulatory male patients of 50 to 75 years of age with stable effort angina class 2 or 3, New York Heart Association (NYHA) classification,[10] treated with 180 mg diltiazem a day and sublingual glyceryl trinitrate alone, were identified and followed up for a run in period of 15 days. Exclusion criteria were conduction defects, left ventricular hypertrophy, or a history of myocardial infarction in the previous three months. At the end of the run in period, patients who developed unstable angina, myocardial infarction, or who required additional treatment with long acting nitrates, β blockers, calcium entry blockers, digoxin, or vasodilators were also excluded.

The remaining patients, continuing on antianginal treatment with diltiazem 180 mg a day and glyceryl trinitrate alone, were assessed by a maximum symptom limited computerised treadmill test according to the Bruce protocol.[11] A history of anginal attacks and sublingual glyceryl trinitrate consumption during the run in period was obtained, and venous blood samples taken for routine biochemical tests. Patients with a positive exercise test (defined as anginal pain plus ST segment depression of ≥ 1 mm, horizontal or down sloping 80 ms beyond the J point, or ST segment depression of ≥ 3 mm without chest pain), and no evidence of renal or hepatic insufficiency were eligible for the study.

TREATMENT GROUPS AND MONITORING

After giving their written informed consent, patients were randomly assigned to receive either diltiazem 180 mg and trimetazidine 60 mg, or diltiazem 180 mg and placebo, each day. A separate randomisation list was prepared for each centre. Gelatin capsules containing 60 mg diltiazem plus 20 mg trimetazidine or placebo (prepared by Serdia Pharmaceuticals, Bombay, India) were identical in taste and appearance. Patients were instructed to take one capsule after breakfast, lunch, and dinner. They were allowed sublingual glyceryl trinitrate 0.5 mg for anginal attacks. An anginal diary was given to each patient to record daily frequency of anginal attacks and glyceryl trinitrate tablet consumption.

ASSESSMENTS AND SIDE EFFECTS

After 28 days' treatment, patients were reassessed by a maximum symptom limited computerised treadmill exercise test, according to the Bruce protocol,[11] at the same time of the day. Exercise was stopped if ST segment depression of 1 mm with chest pain or 3 mm without chest pain occurred, the predicted maximum heart rate was reached, or in the event of arrhythmia, hypotension, dyspnoea, or fatigue. Venous blood samples were collected for routine biochemical tests, and the anginal diaries were retrieved from the patients. The following clinical, exercise, and biochemical variables were assessed at baseline and after 28 days' treatment: number of anginal attacks and glyceryl trinitrate tablets consumed each week; heart rate, blood pressure, and rate–pressure product at rest and exercise; times to onset of angina, 1 mm ST segment depression (horizontal or down sloping 80 ms beyond J point), and peak exercise; maximum work and maximum ST segment depression at peak exercise; total cholesterol, high density lipoprotein (HDL) cholesterol, total triglyceride, fasting blood glucose, and serum creatinine. Concurrent use of other drugs was recorded at baseline and on day 28. Side effects were monitored by asking the patient open ended questions to identify any problems that had occurred since the previous visit.

STATISTICAL ANALYSIS

Sample size was calculated to detect an increase in the number of patients responding to trimetazidine with respect to time to 1 mm ST segment depression, taken as the primary outcome, of at least 40%, that is, from 15% (estimated increase in the placebo group) to 55% ($\alpha = 0.05$, $\beta = 0.01$). Response to treatment was defined as an improvement of ≥ 25% from baseline in clinical and stress test outcomes. Allowing for a 15% dropout rate, we calculated that 32 patients would be needed for each group.

Table 2 Reasons for withdrawal of patients from study, according to study group

Reasons	Trimetazidine and diltiazem		Placebo and diltiazem	
	No of patients	Mean No of days*	No of patients	Mean No of days*
Lack of efficacy	0	–	2	8.0
Adverse reactions†	0	–	2	7.0
Intercurrent illness‡	1	27.0	2	27.0
Refusal to continue	2	5.5	2	6.0
Total patients	3	–	8	–

* After start of study treatment.
† In the placebo group, one patient withdrew because of palpitations, anxiety, and restlessness; and the other because of constipation.
‡Denotes one case of fever in the trimetazidine group; and two patients reporting sick in the placebo group who could not be followed up.

Table 3 Patients with stable angina showing an improvement of at least 25% from baseline, after 28 days' treatment, in clinical and exercise outcomes, according to study group

Outcome	Trimetazidine and diltiazem (n=32) n (%)	Placebo and diltiazem (n=32) n (%)	Difference in response % (95% CI)	p value
Anginal attacks per week	28 (87.5)	15 (46.9)	40.6 (19.9 to 61.3)	< 0.001
Glyceryl trinitrate tablets per week	25 (78.1)	15 (46.9)	31.2 (8.9 to 53.5)	0.01
Exercise time				
At onset of angina	12 (37.5)	5 (15.6)	21.9 (0.9 to 42.9)	< 0.05
At 1 mm ST segment depression	21 (65.6)	9 (28.1)	37.5 (14.9 to 60.1)	0.003
At peak exercise	18 (56.3)	10 (31.3)	25.0 (1.5 to 48.5)	0.04
Maximum work at peak exercise	17 (53.1)	8 (25)	28.1 (5.2 to 51.0)	0.02
Maximum ST segment depression at peak exercise	11 (34.4)	10 (31.3)	3.13	NS

CI, confidence interval.

Results

Response to treatment was analysed on an intention to treat basis, and the categorical data compared by the standard error of difference in proportions. Change in continuous variables was analysed using data on those who completed the study, and compared by *t* test. Significance was defined as a two tailed p value of < 0.05.

Results

Sixty four eligible patients were randomised to the two treatment groups. The baseline characteristics of the patients are shown in table 1, and were balanced between the groups. The majority of patients had moderate functional cardiac disability, and in 12 (19%) the duration of stable angina was more than five years. Nearly half the patients had silent ischaemia, there being no treadmill exercise induced angina at 3 mm ST segment depression. Among those recruited, 53 patients (29 of the 32 in the trimetazidine group, and 24 of the 32 in the placebo group) completed the 28 days of study medication. Three patients in the trimetazidine group, and eight in the placebo group were withdrawn from the study treatment before 28 days'. The reasons for this and the timing are shown in table 2. Adverse events not leading to withdrawal included constipation (two patients in the trimetazidine group, compared to one in the placebo group), increased appetite in one patient in the trimetazidine group, and depression and bradycardia each in one patient in the placebo group.

The number patients in each group who met the criteria of response to treatment (defined as an improvement of at least 25% from baseline in the variable after 28 days' treatment) is summarised in table 3. The intention to treat analysis showed significant difference between treatment groups in clinical and exercise outcomes. As compared to those in the placebo group, the number of patients with a response in the trimetazidine group was greater for anginal attacks per week by 40.6% (95% confidence interval (CI) 19.9 to 61.3; p < 0.001), and for glyceryl trinitrate tablet consumption per week by 31.2% (95% CI 8.9 to 53.5; p = 0.01); greater for exercise time to onset of angina by 21.9% (95% CI 0.9 to 42.9; p = 0.05), for exercise time at 1 mm ST segment depression by 37.5% (95% CI 14.9 to 60.1; p = 0.003), and for peak exercise time by 25% (95% CI 1.5 to 48.5; p = 0.04); and greater for maximum work at peak exercise by 28.1% (95% CI 5.2 to 51.0; p = 0.02). After four weeks' treatment, the number of patients with no exercise induced angina at 3 mm ST segment depression was 13 of 29 with trimetazidine, and 13 of 24 with placebo. The difference was not significant.

The effect of treatment in clinical outcomes is shown in fig 1. As compared to patients in the placebo group, those in the trimetazidine group had a statistically significant improvement in the mean number of anginal attacks of 4.8 per week (95% CI 2.1 to 7.5; p < 0.002), and in mean glyceryl trinitrate tablet consumption of 2.6 per week (95% CI 0.4 to 4.8;

*Figure 1 Mean anginal attacks and glyceryl trinitrate consumption according to study group:—— diltiazem + trimetazidine, - - - diltiazem + placebo. Bars represent 95% confidence intervals. *p < 0.05, †p < 0.01, difference in change from day 0 after treatment between the two groups.*
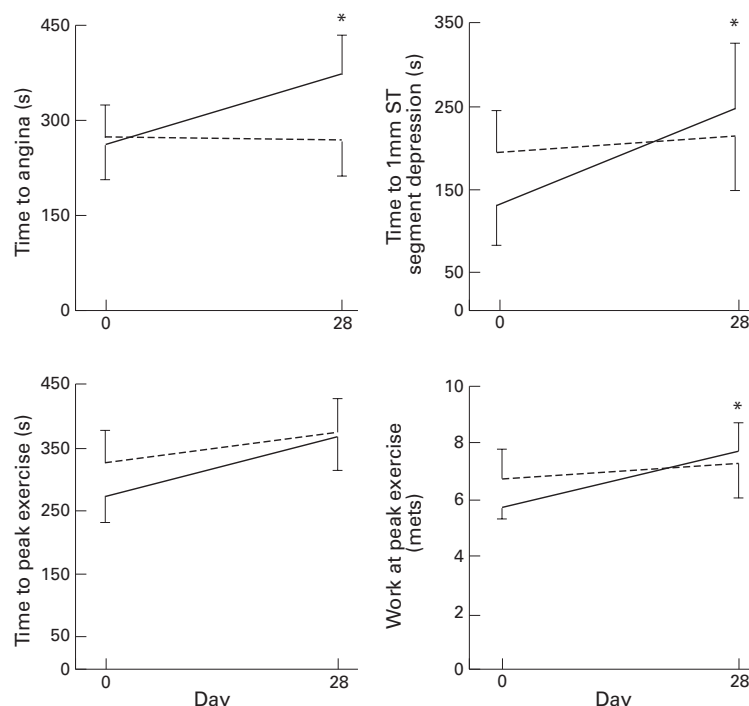
*Figure 2   Mean treadmill exercise outcomes according to study group. —— diltiazem + trimetazidine, - - - diltiazem + placebo. Bars represent 95% confidence intervals. Mets, metabolic equivalents. *p < 0.05, difference in change from day 0 after treatment between the two groups.*

p < 0.05). With regard to treadmill exercise outcomes (fig 2), in comparison to patients in the placebo group, those receiving trimetazidine had a significant improvement in mean exercise time to onset of angina of 113.1 s (95% CI 44.6 to 181.6; p < 0.02), and mean exercise time at 1 mm ST segment depression of 94.2 s (95% CI 5.6 to 182.8; p < 0.05); and an improvement in mean maximum work at peak exercise of 1.4 metabolic equivalents (95% CI 0.3 to 2.4; p < 0.05). Although the increase in mean exercise time at peak exercise was 49.8 s greater with trimetazidine than with placebo, the difference did not reach statistical significance.

There was no significant difference in the mean × 100 (SD) product of heart rate and systolic blood pressure at peak exercise, which increased by 11.3 (43.1) with trimetazidine compared to 17.9 (53.8) in those receiving placebo. The effect of treatment was not significantly different between the two groups with respect to mean resting heart rate, resting systolic and diastolic blood pressure, total cholesterol, HDL cholesterol, total triglyceride, fasting blood glucose, and serum creatinine.

Discussion

Patients with stable angina who had only a partial response to diltiazem in a dose of 180 mg a day had clinically important improvement when trimetazidine was added to their treatment. As shown in table 3 and figs 1 and 2, the benefits were consistent both for clinical features such as weekly anginal attacks and sublingual glyceryl trinitrate consumption, and for treadmill exercise outcomes such as exer-

cise time to onset of angina, exercise time at 1 mm ST segment depression, and maximum work attained at peak exercise.

Although a significantly greater number of patients benefited in exercise time to peak exercise (table 3), by about 50 s (fig 2), this treatment effect did not reach statistical significance. A recent controlled study on combination treatment with trimetazidine and diltiazem has confirmed some of these treatment effects.[12] The lack of an effect of the addition of trimetazidine to diltiazem on resting and exercise heart rate and blood pressure is consistent with the findings in studies with trimetazidine alone,[7] and its mechanism of action.[6]

The conventional treatment of stable angina is with nitrates, β blockers, and calcium entry blockers, and they exert their influence by acting on the determinants of the myocardial oxygen supply–demand balance.[1] Despite their therapeutic efficacy, there are problems with adverse effects, or contraindications to their use, and the fact that they are not universally effective when used alone or in combination.[1] In a placebo controlled study of combination treatment with these agents (nifedipine, isosorbide mononitrate, or both drugs in combination with atenolol) there was no advantage over monotherapy in patients with stable angina.[2] Favourable experience of combination therapy with diltiazem, a calcium entry blocker, and trimetazidine in patients with stable angina encouraged us to study these two drugs.

Diltiazem is effective in controlling symptoms of stable angina,[13] and trimetazidine as a single agent has been shown in controlled studies to have an antianginal efficacy greater than placebo,[7] and equal to nifedipine[8] or propranolol.[9] The two drugs work through different mechanisms. Diltiazem increases coronary blood flow by direct coronary artery vasodilatation, and reduces myocardial oxygen demand by peripheral arterial vasodilatation and a negative inotropic effect.[1] Trimetazidine may act by influencing and partly correcting the metabolic consequences of ischaemia and reperfusion in the myocardium.[6] Increasingly, evidence has focused attention on the cellular metabolic consequences of ischaemia,[14] which, at mitochondrial level, results in a fall in energy to the cytoplasm, depletion of the high energy phosphate compounds ATP and phosphocreatine, and accelerated glycolysis, glycogenolysis, and lactate production.[15] The poor washout causes an accumulation of protons.[16] On reperfusion, the exacerbation of ischaemic injury by toxic free radical species is well established.[17] Trimetazidine has been shown to increase creatine rephosphorylation, increase ATP and phosphocreatine concentrations during reperfusion, and to act as an intracellular buffer to lessen the fall in pH, in the isolated perfused rat heart rendered ischaemic.[18] In the same model, the free radical scavenging effect of trimetazidine has been demonstrated directly,[19] and in red cells treated with free radical generating agents, it reduced malondialdehyde production, a marker of lipid peroxidation by free radicals.[20] The direct cellular action of

trimetazidine is supported by evidence in humans during CABG and PTCA. Oral pretreatment of patients with trimetazidine, and its addition to the cardioplegic solution during CABG, significantly reduced malondialdehyde levels in the coronary sinus, and improved left ventricular function compared to placebo,[21] and intracoronary injection of trimetazidine during PTCA significantly delayed ST segment shift, decreased maximum ST segment shift, and reduced maximum T wave changes compared to placebo, without altering heart rate or intracoronary and systemic pressures.[22] The intracellular metabolic mode of action of trimetazidine may also be clinically useful in chronic heart failure. In a small controlled study of six months' duration on patients with NYHA class 3 and 4 ischaemic cardiomyopathy, stabilised on long acting nitrates, digitalis, diuretics, oral anticoagulants, and antiarrhythmic drugs, trimetazidine significantly reduced dyspnoea and cardiac volume, and increased ejection fraction compared to placebo.[23]

Our protocol in which a combination of diltiazem and trimetazidine was compared with diltiazem plus placebo provided a statistically efficient way of evaluating the short term efficacy and safety of the combination. The adverse events were similar to those associated with diltiazem,[13] and their frequency was not increased by the addition of trimetazidine. Unacceptable haemodynamic side effects such as reflex tachycardia, hypotension, bradycardia, fatigue, and overt left ventricular failure or atrioventricular block found with other drug combinations (such as β blockers with calcium entry blockers or nitrates)[13] did not occur in this trial. The addition of trimetazidine to diltiazem did not affect renal function, blood glucose, or plasma lipids.

The value of the type of combination treatment we studied is that symptoms and exercise stress test outcomes in patients with stable angina improved to a clinically important degree, with minimal side effects. By combining a coronary vasodilator such as diltiazem with trimetazidine, which may correct the cellular metabolic consequences of ischaemia, the combination offers an alternative approach to the management of stable angina. Long term follow up of patients treated with this combination are needed to assess whether the benefits are maintained, and whether long term adverse effects are increased.

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